

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
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 Office, PCT
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 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year)
 14 November 2000 (14.11.00)

International application No.
 PCT/SE00/00664

Applicant's or agent's file reference
 H 2160-1 WO

International filing date (day/month/year)
 06 April 2000 (06.04.00)

Priority date (day/month/year)
 09 April 1999 (09.04.99)

Applicant

LINDFORS, Lennart et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 18 October 2000 (18.10.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Authorized officer

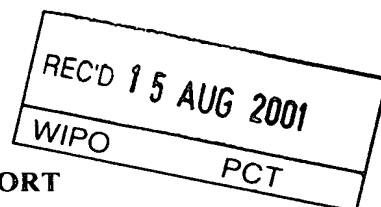
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



| | | |
|--|---|--|
| Applicant's or agent's file reference H 2160-1 WO | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/SE00/00664 | International filing date (day/month/year) 06.04.2000 | Priority date (day/month/year) 09.04.1999 |
| International Patent Classification (IPC) or national classification and IPC ⁷ A 61 K 9/00, A 61 K 47/00, A 61 K 31/66 | | |
| Applicant AstraZeneca AB et al | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 18.10.2000 | Date of completion of this report 03.08.2001 |
| Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5065 S-114 L STOCKHOLM Facsimile No. 08-667 72 88 | Authorized officer Carolina Gómez Lagerlöf/BS Telephone No. 08-782 25 00 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE00/00664

I. Basis of the report

1. With regard to the **elements** of the international application:*

- ☒ the international application as originally filed
- ☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE00/00664

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 45-46

because:

☒ the said international application, or the said claims Nos. 45-46

relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by therapy

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

International application No.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

| | | | |
|-------------------------------|--------|------------------------------|-----|
| Novelty (N) | Claims | <u>3-34, 36, 40-42</u> | YES |
| | Claims | <u>1-2, 35, 37-39, 43-44</u> | NO |
| Inventive step (IS) | Claims | <u></u> | YES |
| | Claims | <u>1-44</u> | NO |
| Industrial applicability (IA) | Claims | <u></u> | YES |
| | Claims | <u>1-44</u> | NO |

The claims disclose a pharmaceutical formulation comprising at least one biphosphonate and one or more additive agents. The claims further disclose the use of the formulation and a process for the preparation of the formulation.

| | | |
|---|----|---------|
| A | WO | 8800829 |
| B | WO | 9705903 |
| C | WO | 9638156 |
| D | WO | 9321907 |
| E | WO | 9852547 |
| F | US | 5296475 |
| G | US | 5344825 |
| H | US | 5650168 |
| I | WO | 9915155 |

Document A discloses a composition containing a bisphosphonate for nasal administration. The composition also contains absorption enhancer. The composition is used to treat, for example, osteoporosis and rheumatoid arthritis.

Document B shows a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter which (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof and a dispersing agent, or (b) comprises a mixture of mono/diglycerides of medium chain fatty acids. Claim 6 shows that the polar drug can be biphosphonate.

...

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Document C relates to the use of alendronate, for the prevention of osteoporosis in early postmenopausal women. Alendronate is administered in a composition containing a carrier that can be lubricants or fatty acids etc.

Document D discloses a preparation containing dichloromethylene bisphosphonic acid that is enteric coated with a film. The film can be selected from a group of polymers that are defined in the claim 3 in the document.

Document E relates to drug-delivery composition for controlled release where the active agent can be bisphosphonate. The composition has an outer layer composed of chitosan.

Document F discloses a pharmaceutical composition comprised of at least one pharmaceutically acceptable methane-diphosphonic acid derivate and at least one macrocyclic polyether.

Document G relates to a pharmaceutical composition for the oral administration of methanediphosphonic acid derivatives containing a cationic macroporous ion exchange resin and pharmaceutically acceptable excipients.

Document H discloses a tablet having a core comprising an effective amount of clodronic acid and an amount of microcrystalline cellulose.

Document I relates to a composition comprising a salt of dichloromethylene bisphosphonic acid and silicified microcrystalline cellulose as an oral solid dosage form.

Thus, a composition comprising at least one of bisphosphonate and at least an additive agent that provide an enhanced absorption of the bisphosphonate is known (refer to document A and B).

The additives mentioned in claim 1 are common additives that are used in pharmaceutical formulations. It is known to use them in formulations together with bisphosphonate. It is not mentioned in documents C-I that the additives promote the adsorption of bisphosphonate.

However, it is not shown in the application that all the additives actually promote the absorption of bisphosphonate.

.../...

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE00/00664

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

It is considered obvious to a person skilled in the art to try to use a common additive to enhance the absorption of bisphosphanate, when it is known that other common additives enhance the absorption of bisphosphanate.

Thus, claims 1-2, 35, 37-39 and 43-44 are not considered to fulfil the requirements of novelty and inventive step. Claims 3-34, 36 and 40-42 are considered to fulfil the requirement of novelty but not that of inventive step.

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09581959

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|---|
| (51) International Patent Classification ⁷ : A61K 9/00, 47/00, 31/66 | A1 | (11) International Publication Number: WO 00/61111 (43) International Publication Date: 19 October 2000 (19.10.00) |
| (21) International Application Number: PCT/SE00/00664 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 9901272-6 9 April 1999 (09.04.99) SE (71) Applicant (for all designated States except US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LINDFORS, Lennart [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). LÖFROTH, Jan-Erik [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). SJÖGREN, Sven [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). UNGELL, Anna-Lena [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). (74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE). | | (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: A PHARMACEUTICAL FORMULATION COMPRISING AN BISPHOSPHONATE AND AN ADDITIVE AGENT PROVIDING AN ENHANCED ABSORPTION OF THE BISPHOSPHONATE (57) Abstract <p>The present invention provides pharmaceutical formulations comprising at least one bisphosphonate and an additive consisting of one or more absorption enhancing agents. The said pharmaceutical formulations are useful for the inhibition of bone resorption and for the treatment and prevention of osteoporosis.</p> | | |

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A PHARMACEUTICAL FORMULATION COMPRISING AN BISPHOSPHONATE AND AN ADDITIVE AGENT PROVIDING AN ENHANCED ABSORPTION OF THE BISPHOSPHONATE

TECHNICAL FIELD

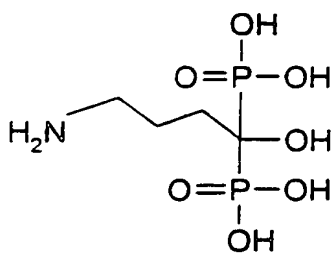
5 The present invention relates to pharmaceutical formulations comprising bisphosphonates. The invention also relates to a process for preparing such pharmaceutical formulations, to the use of such pharmaceutical formulations for inhibition of bone resorption and for the treatment and prevention of osteoporosis.

10

BACKGROUND ART

Bisphosphonates

15 Bisphosphonates are carbon-substituted pyrophosphate analogues that include potent inhibitors of bone resorption, such as alendronate (4-amino-1-hydroxybutylidene-1,1-biphosphonic acid) (Sato et al. (1991) J. Clin. Invest. 88, 2095-2105).



alendronate

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The oral bioavailability of bisphosphonates (etidronate; clodronate; pamidronate; alendronate) in humans lies between 1% and 10% according to Lin (Bone 18, 75-85, 1996) and absorption is diminished when given with meals, especially in the presence of calcium. Therefore bisphosphonates should never be given at mealtime and never together with milk or dairy products according to Fleisch (Bisphosphonates in bone disease, Stampfli & Co., Bern 1993, p.50, and references cited therein). In Dowty M.E. et al. Pharm. Sci. Suppl., Vol 1, No 1: 448 (1998) the low permeability of risedronate is disclosed.

The oral bioavailability of alendronate has been studied by Gertz et al. (Clinical Pharmacology & Therapeutics, vol. 58, pp. 288-298, 1995). It was found that taking alendronate either 60 or 30 minutes before breakfast reduced bioavailability by 40% relative to a 2-hour wait before a meal. Taking alendronate either concurrently with or 2 hours after breakfast drastically (>85%) impaired availability. A practical dosing recommendation, derived from these findings was that patients should take the drug with water after an overnight fast and at least 30 min before any other food or beverage.

Moreover, the labeling information on an existing commercial formulation of alendronate (FOSAMAX[®]) contains a warning that the formulation, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa. This clearly shows that a solution to the problems associated with the poor and variable absorption of orally administered bisphosphonates known for a long time has not yet been found.

Consequently, there is a need for pharmaceutical formulations comprising bisphosphonates, such as alendronate, which reduces the above mentioned drawbacks and allows the patient to take the medicament more conveniently, e.g. together with food intake.

Absorption enhancers

Pharmaceutical excipients may be classified as functional or not-functional (M E Aulton: Pharmaceutics - The science of dosage form design, Churchill Livingstone 1988, Hong Kong). Non-functional excipients are, e.g., binders, fillers, dryers etc and are used to fulfill pharmaceutical technology aspects of the formulation as size, hardness, appearance (e.g. colour) etc. Functional excipients on the other hand are utilized, e.g. to achieve certain types of release profiles such as immediate release, extended release, controlled release etc by the use of rapidly or slowly hydrating, swelling, eroding, etc polymer materials; to achieve fast dissolution of the drug by incorporating surface active substances; to achieve control of the pH in the formulation or in the immediate environment of the drug by the usage of buffers in the formulation; etc.

Another important aspect of excipients is the influence from functional excipients on the biological environment that can be obtained with certain substances, often called enhancers in the literature, by for example changing the permeability of the biological membrane, to inhibit complex formation with biological substances present (e g proteins, lipids, bile salt, ions), etc. The rationale for the use of such excipients is then to achieve, e g higher availability, less variation in absorption due to, e g food interactions (Charman WN et al. J Pharm Res 86 (3): 269-282 (1997)) avoidance of instability in GI-environment, to diminish drug influence on membrane integrity etc. Comprehensive reviews on the effect of enhancer agents and their use in pharmaceutical formulations have been presented by E J van Hoogdalem et al (Pharm Theor vol 44, 407-443 (1989)); by S Muranishi et al (Crit Rev Ther Drug Carrier Syst vol 7, 1-33 (1990)); by E S Swenson and W J Curatolo (Adv Drug Deliv Rev vol 8, 39-92 (1998)); in drug Absorption Enhancement (Ed: A B G de Boer, Harwood Academic Publishers 1994); in Baughman RA et al Circulation 98 (16): 1610-1615 (1998); in Bai JP et al, Crit Rev Therap Drug Carrier Syst 12(4): 339-371 (1995); in Bowe CL et al, Proc Nat Acad Sci 94 (22): 12218-23 (1997); in Chao AC et al, J Pharm Sci 87(11): 1395-1399 (1998); in Chao AC et al, J Drug Targeting 6(1): 37-43 (1998); and in Fix JA. J Pharm Sci 85(12) 1282-1285 (1996).

In many circumstances the enhancers combine several different effects. However, the degree of influence on the biological environment is seldom known *á priori*, and mechanisms behind the effects are obscure and difficult to ascertain *in-vivo*. The different types of such functional excipients includes e g lipids, chelators, and polymers which all may act, e g by preventing or enhancing complexation with species from the biological environment (e g proteins, bile salts, lipids, ions like Ca^{2+} etc), by influencing the membrane permeability in a reversible or irreversible manner, by presenting the drug in small particulate form and thereby avoiding high local concentrations that might be irritating near the membranes of the drug, etc.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that the absorption of bisphosphonates can be substantially improved by incorporating one or more additives in pharmaceutical formulations containing bisphosphonates. The use of additives as enhancers will result in positive advantageous effects, such as enhanced and/or less variable absorption when bisphosphonates, e.g. alendronate, is given by different administration routes, such as the oral, the rectal, the buccal, the nasal and the pulmonary route. It will allow the patient to take the medicament more conveniently, e.g. together with food intake. It will also reduce side-effects as local irritation of, e.g. the upper gastrointestinal mucosa.

Therefore, the present invention provides a pharmaceutical formulation comprising at least one bisphosphonate and one or more additives selected from the group consisting of

- a surfactant, such as a nonionic surfactant, e.g., a sorbitan ester (Span series), a polysorbate (Tween series), a poloxyethylated glycol monoether (like the Brij series), a polyoxylated alkyl ester (Myrj series), a polyoxyethylated alkyl phenol (like the Triton series), an alkyl glucoside, like sugar glycosides, e.g., dodecylmaltoside, sugar fatty acid esters, e.g. sucrose laurate, sucrose monostearate and saponins;
- an ampholytic surfactant, e.g., a betaine;
- an anionic surfactant, e.g., a sulphated fatty alcohol, a sulphated polyoxyethylated alcohol, others like dioctyl sulphosuccinate;
- a cationic surfactant, e.g., an ammonium compound;
- a bile salt, such as a dihydroxy bile salt like sodium deoxycholate, a trihydroxy bile salt like sodium glycocholate and fusidates, e.g., sodium dihydrofusidate;
- a soap and a fatty acid, and a salt thereof, e.g. octanoic acid, decanoic acid and sodium decanoate;
- a lipid (with the exception of those disclosed in PCT application no. SE98/01790), such as a phospholipid, e.g., DPPC and DMPC;
- an oil, e.g., soy bean oil and sunflower oil;
- an enamine, such as DL-phenylalanine and ethylacetoacetate enamine;
- a chelating agent, e.g., EDTA, EGTA, and citric acid;
- a phenothiazine, such as chlorpromazine;

- a fatty acid derivative of carnitine and peptides, e.g., palmitoyl-DL-carnitine;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL - α -glycerophosphate and 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;
- a product from Maillard reactions, i.e. a product obtained by reacting sugars with amino acids, e.g., a compound from a glucoselysine reaction;
- a polymer, such as a polyacrylic acid, e.g., Carbopol[®], polycarbophil;
- a chitosan and a chitosan derivative; and
- a block copolymer, e.g., a poloxamer, poloxamine, and meroxapol.
- a biodegradable polymer, e.g. polyactic acid, polyglycolic acid, and copolymers of these.

Suitable intended combinations of the enhancing agents are, but are not limited to:

- Lipids (also those disclosed in PCT application no. SE 98/01790) and surfactants, eg monoolein and sodium taurocholate, monoolein and Tween 80 (polyoxyethylene (20) sorbitan mono-oleate, also named polysorbate 80);

Lipids of non-phospholipids character (also those disclosed in SE 98/01790) and phospholipids, e.g. medium chain glycerides and lecithins;

Lipids (also those disclosed in SE 98/01790) and block copolymers, e.g. monoolein and Pluronic F 127 (which is the triblock copolymer poloxamer 407 of polyoxyethylene/polyoxypropylene/polyoxyethylene);

Surfactants and oils, e.g. sucrose fatty acid esters and soy bean oil; and

Polymers and lipids, e.g. polycarbophil and monoolein.

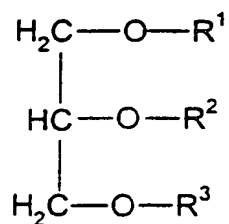
- The combinations might be in the form of emulsions and microemulsions comprising e.g. monoolein/triglyceride/water or isopropyl myristate/lecithin/water.

Preferred additives of the invention are

- nonionic surfactants, such as sugar glycosides and sugar fatty acid esters;
- lipids, such as a phospholipid e g DPPC and DMPC;
- an oil, such as soy bean oil and sunflower oil;
- 5 - a chelating agent, e g EDTA, EGTA, citric acid;
- a fatty acid derivative of carnitine or a peptide; e.g. palmitoyl-DL-carnitine;
- polymer, such as polyacrylic acid, e g Carbopol, polycarbophil
- a block copolymer, e g a poloxamer, poloxamine and meroxapol;
- a saponin;
- 10 - the combinations listed above.

Lipids referred to above as disclosed in PCT application no. SE 98/01790 are a medium chain glyceride or a mixture of medium chain glycerides, particularly those having the formula

15



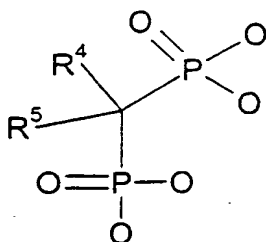
wherein R^1 , R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one of R^1 , R^2 and R^3 is an alkanoyl group.

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The dosage form used may be a solid, semisolid or liquid preparation prepared by techniques which are known *per se*. Usually the active substance will constitute between 0.001% and 99% by weight of the preparation, preferably 0.003 to 1.3 % by weight, most preferably 0.1 to 1%.

25

Preferably, the bisphosphonate has the general formula II



II

wherein

5 R⁴ is H, OH or Cl; and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- 10 (b) halogen;
- (c) arylthio, preferably chlorosubstituted;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

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Alkyl groups in alkylamino and dialkylamino may have 1 to 5 carbon atoms and may be combined independently in the dialkylamino group.

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The term "heterocyclyl" means a saturated or unsaturated 5 to 7- membered heterocyclic group with one or two rings and 1 to 3 heteroatoms, independently chosen from N, O and S.

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Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphthyl.

The term "substituted aryl" denotes an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

5 Compounds of the formula II include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),
N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid
(mildronate,olpadronate),
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate),
10 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),
1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate),
1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid,
1-hydroxy-2-(1-imidazolyl)ethylidene-1,1-bisphosphonic acid (zoledronate),
1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid
15 (minodronate),
1-(4-chlorophenylthio)methylidene-1,1-bisphosphonic acid (tiludronate),
1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate)
and pharmaceutically acceptable salts thereof.

20

The most preferred compounds of the formula II are 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate) and its pharmaceutically acceptable salts.

In a preferred form, the pharmaceutical formulation according to the invention is adapted
25 for oral administration and may be given during fasted or fed conditions.

In the preparation of pharmaceutical formulations according to the invention in the form of dosage units for oral administration, the bisphosphonate and the absorption enhancing agent may be filled into soft or hard gelatine or cellulose capsules; mixed with solid,
30 powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient; with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate

and polyethylene glycol waxes. The mixture is then processed into particulate forms, granules or pressed into tablets.

In one embodiment of the invention the bisphosphonate and the additive is mixed into a suitable form considering that a particulate (solid, semisolid or liquid) form might be preferably chosen to avoid the presentation of the drug in high local concentrations that might be irritating at the mucosal membranes. Such particulate forms can be obtained by well known procedures, such as dispersing the bisphosphonate as a micronised powder (< 10 µm) in a suitable medium like sesam oil, soya oil etc, or by forming a carrier/drug system in particulate form. Micronised bisphosphonates or carrier/drug systems can be prepared by techniques such as but not limited to dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, spray freeze drying, electrospraying, supercritical crystallisation (RESS or GAS methods), emulsion solvent evaporation, emulsion solvent extraction and emulsion solvent diffusion.

This suspension of the bisphosphonate in oil or the carrier/bisphosphonate system is then administered orally as a suspension or in capsules.

Suitable daily doses of bisphosphonates in therapeutic treatment of humans are about 0.001 to 100 mg/kg body weight at peroral administration, preferably 0.001 to 10 mg/kg, most preferably 0.005 to 0.3 mg/kg.

The enhancing agent, or the combination of enhancing agents, and a suitable carrier or non-functional excipients when needed will constitute between 0.1 to 99.9% by weight of the preparation, preferably between 80% to 99.9% by weight.

The pharmaceutical formulations according to the invention are useful for inhibiting bone resorption and thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. The pharmaceutical formulations according to the invention are further useful for the

treatment of hypercalcaemia. Consequently, the use of the said pharmaceutical formulations for treating these conditions are additional aspects of the invention.

5 In another aspect the invention provides a process for the preparation of a pharmaceutical formulation according to the invention, said process comprising forming a mixture of (i) bisphosphonate, (ii) an additive, and (iii) a pharmaceutically acceptable carrier.

10 In a further aspect the invention provides the use of bisphosphonate in conjunction with an absorption enhancing agent for the manufacture of a medicament for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. Preferably, the said medicament is adapted for oral administration.

15 In yet a further aspect the invention provides a method for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary
20 osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis, which method comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to the invention. Preferably, the said pharmaceutical formulation is administered orally.

25 **Biological evaluation**

The effectiveness of formulations according to the present invention to prevent bone loss has been analyzed in studies using intact young growing rat model, developed and well established to predict the effectiveness of bisphosphonates in later clinical practise.

30

Results

ED₅₀ values obtained in the intact rat model show that orally administered formulations according to the invention that have been tested are more potent than equimolar bisphosphonate alone.

5 In a 14-day study of intact young growing rats a clear dose-response effect of enhancer was found. No effects were found for bisphosphonate in saline and given per os.

The effects on bone density obtained with enhancer/bisphosphonate was similar to what was obtained with bisphosphonate given subcutaneously, while no effect was found for bisphosphonate in saline given per os.

All rats appeared normal and gained normal weight.

10

Conclusions

The rat studies strongly support the concept that enhancers as suggested in the present specification can increase the oral bioavailability of a bisphosphonate as disclosed in the present specification even in the presence of food.

15

Examples

Examples of pharmaceutical formulations according to the invention:

5 *Formulation 1*

| | |
|--------------------------------------|---------|
| Alendronate | 2.3 mg |
| Caprylic acid, sodium salt | 11.5 mg |
| 50 mM Tris with 100 mM NaCl (buffer) | 1.0 g |

10 Approx. 2.3 mg alendronate and 11.5 mg caprylic acid was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 2

| | |
|--------------------------------------|---------|
| Alendronate | 2.3 mg |
| 15 Monoolein | 11.5 mg |
| Tween 80 | 11.5 mg |
| 50 mM Tris with 100 mM NaCl (buffer) | 1.0 g |

 Approx. 2.3 mg alendronate and 11.5 mg monoolein was dissolved in buffer containing
20 Tween 80 and pH adjusted to 7.5 using sodium hydroxide.

Formulation 3

| | |
|--|---------|
| Alendronate | 2.3 mg |
| Quil A | 11.5 mg |
| 25 50 mM Tris with 100 mM NaCl (buffer) | 1.0 g |

 Approx. 2.3 mg alendronate and 50 mg Quil A was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 4

| | |
|--------------------------------------|--------|
| Alendronate | 2.3 mg |
| Carbopol 934P | 5.0 mg |
| 50 mM Tris with 100 mM NaCl (buffer) | 1.0 g |

Approx. 2.3 mg alendronate and 5.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 5

| | |
|--------------------------------------|---------|
| Alendronate | 2.3 mg |
| Carbopol 934P | 15.0 mg |
| 50 mM Tris with 100 mM NaCl (buffer) | 1.0 g |

Approx. 2.3 mg alendronate and 15.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 6

| | |
|--------------------------------------|--------|
| Alendronate | 2.3 mg |
| Isopropylmyristate | 630 mg |
| Lecithin (Epicuron 200) | 270 mg |
| 50 mM Tris with 100 mM NaCl (buffer) | 100 mg |

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and lecithin (70/30 w/w) while vortexing.

Formulation 7

| | |
|--------------------|--------|
| Alendronate | 2.3 mg |
| Isopropylmyristate | 450 mg |
| Tween 21 | 450 mg |

50 mM Tris with 100 mM NaCl (buffer) 100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and Tween 21 (50/50 w/w) while vortexing.

Formulation 8

Alendronate 2.3 mg

Monoolein 630 mg

10 Soybean triglycerides 270 mg

50 mM Tris with 100 mM NaCl (buffer) 100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of monoolein and soybean triglycerides (70/30 w/w) while vortexing.

Formulation 9

Alendronate 2.3 mg

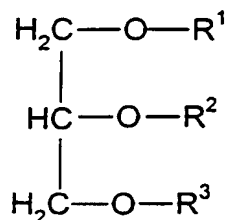
Soybean triglycerides 1.0 g

2.3 mg alendronate was added to soybean triglycerides and micronized using ultrasonication while cooling on ice.

CLAIMS

1. A pharmaceutical formulation comprising at least one bisphosphonate and one or more of an additive agent, said additive agent being present in an amount sufficient to provide an enhanced absorption of the bisphosphonate, and said additive being a substance selected from the group consisting of

- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid with the exception of a medium chain glyceride or a mixture of medium chain glycerides having the formula



wherein R^1 , R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one of R^1 , R^2 and R^3 is an alkanoyl group.

- an oil;
- an enamine;
- a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL - α -glycerophosphate and 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;

- a product from Maillard reactions;
- a polymer, such as a block copolymer and a biodegradable polymer;
- a chitosan and a chitosan derivative;

- 5 2. A pharmaceutical formulation according to claim 1, wherein the additive is a nonionic surfactant.
3. A pharmaceutical formulation according to claim 2, wherein the nonionic surfactant is a sugar glycoside or a sugar fatty acid ester.
- 10 4. A pharmaceutical formulation according to claim 1, wherein the additive is a lipid.
5. A pharmaceutical formulation according to claim 4, wherein the lipid is a phospholipid.
- 15 6. A pharmaceutical formulation according to claim 1, wherein the additive is an oil.
7. A pharmaceutical formulation according to claim 6, wherein the oil is soy bean oil or sunflower oil.
- 20 8. A pharmaceutical formulation according to claim 1, wherein the additive is a chelating agent.
9. A pharmaceutical formulation according to claim 8, wherein the chelating agent is
25 EDTA, EGTA or citric acid.
10. A pharmaceutical formulation according to claim 1, wherein the additive is a fatty acid derivative of carnitine or a peptide.
- 30 11. A pharmaceutical formulation according to claim 10, wherein the additive of the fatty acid derivative of carnitine or a peptide is palmitoyl-DL-carnitine.

12. A pharmaceutical formulation according to claim 1, wherein the additive is a polymer.
13. A pharmaceutical formulation according to claim 12, wherein the polymer is a polyacrylic acid.
14. A pharmaceutical formulation according to claim 1, wherein the additive is a block copolymer.
15. A pharmaceutical formulation according to claim 14, wherein the block copolymer is a poloxamer, a poloxamine or meroxapol.
16. A pharmaceutical formulation according to claim 1, wherein the additive is a saponin.
17. A pharmaceutical formulation according to claim 1, wherein the additive is a biodegradable polymer.
18. A pharmaceutical formulation according to claim 17, wherein the biodegradable polymer is polyactid acid or polyglycolic acid.
19. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a surfactant.
20. A pharmaceutical formulation according to claim 19, wherein the combination of the lipid and the surfactant is monoolein and sodium taurocholate, or monoolein and Tween 80.
21. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid of non-phospholipid character and a phospholipid.
22. A pharmaceutical formulation according to claim 21, wherein the combination of the lipid of non-phospholipid character and the phospholipid is a medium chain glyceride and a lecithin.

23. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a block copolymer.

24. A pharmaceutical formulation according to claim 23, wherein the combination of the lipid and the block copolymer is monoolein and Pluronic F 127.

25. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a surfactant and an oil.

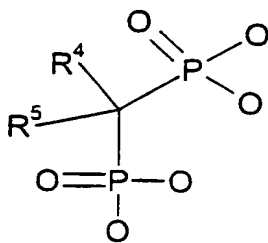
26. A pharmaceutical formulation according to claim 25, wherein the combination of the surfactant and the oil is a sucrose fatty acid ester and soy bean oil.

27. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a polymer and a lipid.

28. A pharmaceutical formulation according to claim 27, wherein the combination of the polymer and the lipid is polycarbophil and monoolein.

29. A pharmaceutical formulation according to claim 1, wherein the combination of additives is chosen to form an emulsion or a microemulsion.

30. A pharmaceutical formulation according to any one of claims 1 to 29 wherein the said bisphosphonate has the formula II



II

wherein

R⁴ is H, OH or Cl, and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- 5 (b) halogen;
- (c) arylthio or chlorosubstituted arylthio;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

10

31. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R⁴ is H or OH and

15

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2
- 20 heteroatoms.

32. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

25

R⁴ is OH and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or
- 30 (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

33. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate is
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),
N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid
5 (mildronate,olpadronate),
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid
(ibandronate),
1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),
1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate),
10 1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid,
1-hydroxy-2-(1-imidazolyl)ethylidene-1,1-bisphosphonic acid (zoledronate),
1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid
(minodronate),
1-(4-chlorophenylthio)methylidene-1,1-bisphosphonic acid (tiludronate),
15 1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate)
and pharmaceutically acceptable salts there of.
34. A pharmaceutical formulation according to claim 33 wherein the bisphosphonate is
20 alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid) or
pharmaceutically acceptable salts there of.
35. A pharmaceutical formulation according to any one of claims 1 to 34 which is adapted
for oral administration.
25
36. A pharmaceutical formulation according to any one of claims 1-35 which is adapted for
non colonic delivery.
37. A pharmaceutical formulation according to any one of claims 1 to 36 for inhibiting
30 bone resorption.

38. A pharmaceutical formulation according to any one of claims 1 to 36 for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

39. A pharmaceutical formulation according to any of the preceeding claims wherein the formulation is in particulate form.

40. A pharmaceutical formulation according to claim 39 wherein the particulate form is solid or semisolid.

41. A pharmaceutical formulation according to any of claims 39 and 40 wherein the bisphosphone is in the form of micronized powder.

42. A process for the preparation of a pharmaceutical formulation according to any one of claims 1 to 40, comprising forming a mixture of (i) at least one bisphosphonate, (ii) an additive and (iii) a pharmaceutically acceptable carrier.

43. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the inhibition of bone resorption.

44. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, or cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

45. A method for inhibition of bone resorption which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 41.

46. A method for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis, which comprises administering to a mammal, including man, in need of such treatment an effective
5 amount of a pharmaceutical formulation according to any one of claims 1 to 41.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00664

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/00, A61K 47/00, A61K 31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| P,X | WO 9918972 A1 (ASTRA AKTIEBOLAG), 22 April 1999 (22.04.99) -- | 1-46 |
| X | WO 8800829 A1 (LEO PHARMACEUTICAL PRODUCTS LTD.), 11 February 1988 (11.02.88), page 3, line 6 - line 28; page 4, line 18 - page 7, line 26, abstract, claims -- | 1-46 |
| X | WO 9705903 A2 (DANBIOSYST UK LIMITED), 20 February 1997 (20.02.97), abstract, claims -- | 1-46 |
| X | WO 9638156 A1 (MERCK & CO., INC.), 5 December 1996 (05.12.96), page 3, line 28 - page 5, line 13 -- | 1-46 |

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 July 2000

Date of mailing of the international search report

02-08-2000

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00664

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | WO 9321907 A1 (LEIRAS OY), 11 November 1993 (11.11.93), page 1, line 29 - page 4, line 15, claims -- | 1-46 |
| X | WO 9852547 A1 (DANBIOSYST UK LIMITED), 26 November 1998 (26.11.98), page 9, line 1 - page 17, line 26, claim 14 -- | 1-46 |
| X | US 5296475 A (GERARD FLESCHE ET AL), 22 March 1994 (22.03.94) -- | 1-46 |
| X | US 5344825 A (SATISH C. KHANNA ET AL), 6 Sept 1994 (06.09.94) -- | 1-46 |
| X | US 5650168 A (WALTER PREIS ET AL), 22 July 1997 (22.07.97) -- | 1-46 |
| X | WO 9915155 A1 (LEIRAS OY), 1 April 1999 (01.04.99), claims -- ----- | 1-46 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 45-46
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE00/00664

Claims 45-46 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 00/00664

| Patent document cited in search report | | | Publication date | Patent family member(s) | | | Publication date |
|--|---------|----|------------------|-------------------------|----------|-----|------------------|
| WO | 9918972 | A1 | 22/04/99 | AU | 9469198 | A | 03/05/99 |
| | | | | SE | 9703691 | D | 00/00/00 |
| WO | 8800829 | A1 | 11/02/88 | DK | 153988 | A | 22/03/88 |
| | | | | EP | 0276288 | A | 03/08/88 |
| | | | | JP | 1500754 | T | 16/03/89 |
| WO | 9705903 | A2 | 20/02/97 | AU | 707587 | B | 15/07/99 |
| | | | | AU | 6705996 | A | 05/03/97 |
| | | | | CA | 2227764 | A | 20/02/97 |
| | | | | EP | 0843558 | A | 27/05/98 |
| | | | | GB | 2318056 | A,B | 15/04/98 |
| | | | | GB | 9516268 | D | 00/00/00 |
| | | | | GB | 9801507 | D | 00/00/00 |
| | | | | JP | 11510506 | T | 14/09/99 |
| | | | | NO | 980047 | A | 06/01/98 |
| WO | 9638156 | A1 | 05/12/96 | AU | 709196 | B | 26/08/99 |
| | | | | AU | 5882496 | A | 18/12/96 |
| | | | | BG | 102060 | A | 31/07/98 |
| | | | | BR | 9609020 | A | 06/07/99 |
| | | | | CA | 2222318 | A | 05/12/96 |
| | | | | CN | 1192685 | A | 09/09/98 |
| | | | | CZ | 9703811 | A | 17/06/98 |
| | | | | EP | 0828496 | A | 18/03/98 |
| | | | | IL | 118422 | D | 00/00/00 |
| | | | | JP | 10506648 | T | 30/06/98 |
| | | | | NO | 975527 | A | 01/12/97 |
| | | | | PL | 323669 | A | 14/04/98 |
| | | | | SK | 159597 | A | 03/06/98 |
| | | | | ZA | 9604465 | A | 11/12/96 |
| WO | 9321907 | A1 | 11/11/93 | AT | 143802 | T | 15/10/96 |
| | | | | AU | 671830 | B | 12/09/96 |
| | | | | AU | 3955093 | A | 29/11/93 |
| | | | | CA | 2134196 | A | 11/11/93 |
| | | | | CZ | 282871 | B | 12/11/97 |
| | | | | CZ | 9402614 | A | 15/02/95 |
| | | | | DE | 637236 | T | 06/07/95 |
| | | | | DE | 69305335 | D,T | 30/04/97 |
| | | | | DK | 637236 | T | 17/03/97 |
| | | | | EP | 0637236 | A,B | 08/02/95 |
| | | | | ES | 2094539 | T | 16/01/97 |
| | | | | FI | 944961 | A | 21/10/94 |
| | | | | GR | 3022249 | T | 30/04/97 |
| | | | | HK | 13097 | A | 14/02/97 |
| | | | | HU | 74572 | A | 28/01/97 |
| | | | | HU | 9403067 | D | 00/00/00 |
| | | | | IL | 105403 | A | 10/03/98 |
| | | | | JP | 7505898 | T | 29/06/95 |
| | | | | NO | 944001 | A | 21/10/94 |
| | | | | SE | 501389 | C | 30/01/95 |
| | | | | SE | 9201299 | A | 25/10/93 |
| | | | | US | 5525354 | A | 11/06/96 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 00/00664

| Patent document cited in search report | | | Publication date | Patent family member(s) | | Publication date |
|---|---------|----|---------------------|----------------------------|-------------|---------------------|
| WO | 9852547 | A1 | 26/11/98 | AU | 7664298 A | 11/12/98 |
| | | | | GB | 9710699 D | 00/00/00 |
| US | 5296475 | A | 22/03/94 | AU | 3019292 A | 24/06/93 |
| | | | | CA | 2085713 A | 20/06/93 |
| | | | | EP | 0550385 A | 07/07/93 |
| | | | | JP | 5255116 A | 05/10/93 |
| US | 5344825 | A | 06/09/94 | AT | 183096 T | 15/08/99 |
| | | | | AU | 665814 B | 18/01/96 |
| | | | | AU | 3696193 A | 21/10/93 |
| | | | | CA | 2093946 A | 16/10/93 |
| | | | | DE | 59309727 D | 00/00/00 |
| | | | | EP | 0566535 A,B | 20/10/93 |
| | | | | SE | 0566535 T3 | |
| | | | | FI | 931633 A | 16/10/93 |
| | | | | IL | 105382 A | 15/06/98 |
| | | | | JP | 6009408 A | 18/01/94 |
| | | | | MX | 9302151 A | 01/10/93 |
| | | | | NO | 931367 A | 18/10/93 |
| | | | | NZ | 247398 A | 26/07/95 |
| | | | | ZA | 9302613 A | 26/10/93 |
| US | 5650168 | A | 22/07/97 | AT | 128 U | 27/03/95 |
| | | | | AT | 128363 T | 15/10/95 |
| | | | | AU | 687744 B | 05/03/98 |
| | | | | AU | 4702093 A | 12/12/94 |
| | | | | BR | 9307859 A | 09/01/96 |
| | | | | CA | 2162470 A,C | 24/11/94 |
| | | | | CN | 1041797 B | 27/01/99 |
| | | | | CN | 1095267 A | 23/11/94 |
| | | | | CZ | 9500100 A | 18/10/95 |
| | | | | DE | 9307393 U | 04/11/93 |
| | | | | DE | 59300688 D | 00/00/00 |
| | | | | DK | 625355 T | 27/12/95 |
| | | | | EP | 0625355 A,B | 23/11/94 |
| | | | | SE | 0625355 T3 | |
| | | | | EP | 0697890 A | 28/02/96 |
| | | | | ES | 2065313 T | 16/02/95 |
| | | | | FI | 945313 A | 13/12/94 |
| | | | | GR | 3017547 T | 31/12/95 |
| | | | | GR | 94300095 T | 31/01/95 |
| | | | | HU | 70214 A | 28/09/95 |
| | | | | HU | 9403160 D | 00/00/00 |
| | | | | IL | 106743 D | 00/00/00 |
| | | | | JP | 8509697 T | 15/10/96 |
| | | | | NO | 944405 A | 24/11/94 |
| | | | | NZ | 254765 A | 24/02/97 |
| | | | | PL | 173026 B | 30/01/98 |
| | | | | PL | 307133 A | 02/05/95 |
| | | | | SK | 4895 A | 08/01/97 |
| | | | | WO | 9426310 A | 24/11/94 |
| | | | | ZA | 9306041 A | 20/02/95 |
| | | | | DE | 4322057 A | 12/01/95 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 00/00664

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|-----------------------------|----------------------|
| WO 9915155 A1 | 01/04/99 | AU 9268598 A FI 973733 A | 12/04/99 20/03/99 |
| <hr/> | | | |

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum) H 2160-1 WO

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| AstraZeneca AB S-151 85 Södertälje Sweden | <input type="checkbox"/> This person is also inventor. Telephone No. +46 8 553 260 00 Facsimile No. +46 8 553 288 20 Teleprinter No. |
| State (that is, country) of nationality: SE | State (that is, country) of residence: SE |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box | |
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| LINDBFORS, Lennart AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden | This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i> |
| State (that is, country) of nationality: SE | State (that is, country) of residence: SE |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box | |
| <input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet. | |
| Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE | |
| The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative | |
| Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> | |
| Global Intellectual Property, Patents AstraZeneca AB S-151 85 Södertälje Sweden | Telephone No. +46 8 553 260 00 Facsimile No. +46 8 553 288 20 Teleprinter No. |
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LÖFROTH, Jan-Erik
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

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Sweden

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
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State (that is, country) of residence:
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This person is applicant for the purposes of:

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
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- ☐ inventor only (If this check-box is marked, do not fill in below.)

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| <input type="checkbox"/> BA Bosnia and Herzegovina | <input type="checkbox"/> MD Republic of Moldova |
| <input type="checkbox"/> BB Barbados | <input type="checkbox"/> MG Madagascar |
| <input type="checkbox"/> BG Bulgaria | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
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| <input type="checkbox"/> BY Belarus | <input type="checkbox"/> MW Malawi |
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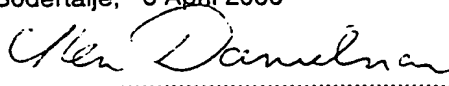
| Box No. VI PRIORITY CLAIM | | <input type="checkbox"/> Further priority claims are indicated in the Supplemental Box. | | |
|---|----------------------------------|---|--|--|
| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
| | | national application: country | regional application: * regional Office | international application: receiving Office |
| item (1) 09 April 1999 (09.04.1999) | 9901272-6 | Sweden (SE) | | |
| item (2) | | | | |
| item (3) | | | | |

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

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| | | Date (day/month/year) 22 November 1999 | Number SE99/00458 |

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| This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 14 claims : 8 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 27 | This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input checked="" type="checkbox"/> copy of general power of attorney, reference number, if any: GF290/2000, GF291/2000 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): ITS Report SE99/00458 |
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| Södertälje, 6 April 2000  Sten Danielsson Global Intellectual Property, Patents, AstraZeneca AB | |

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